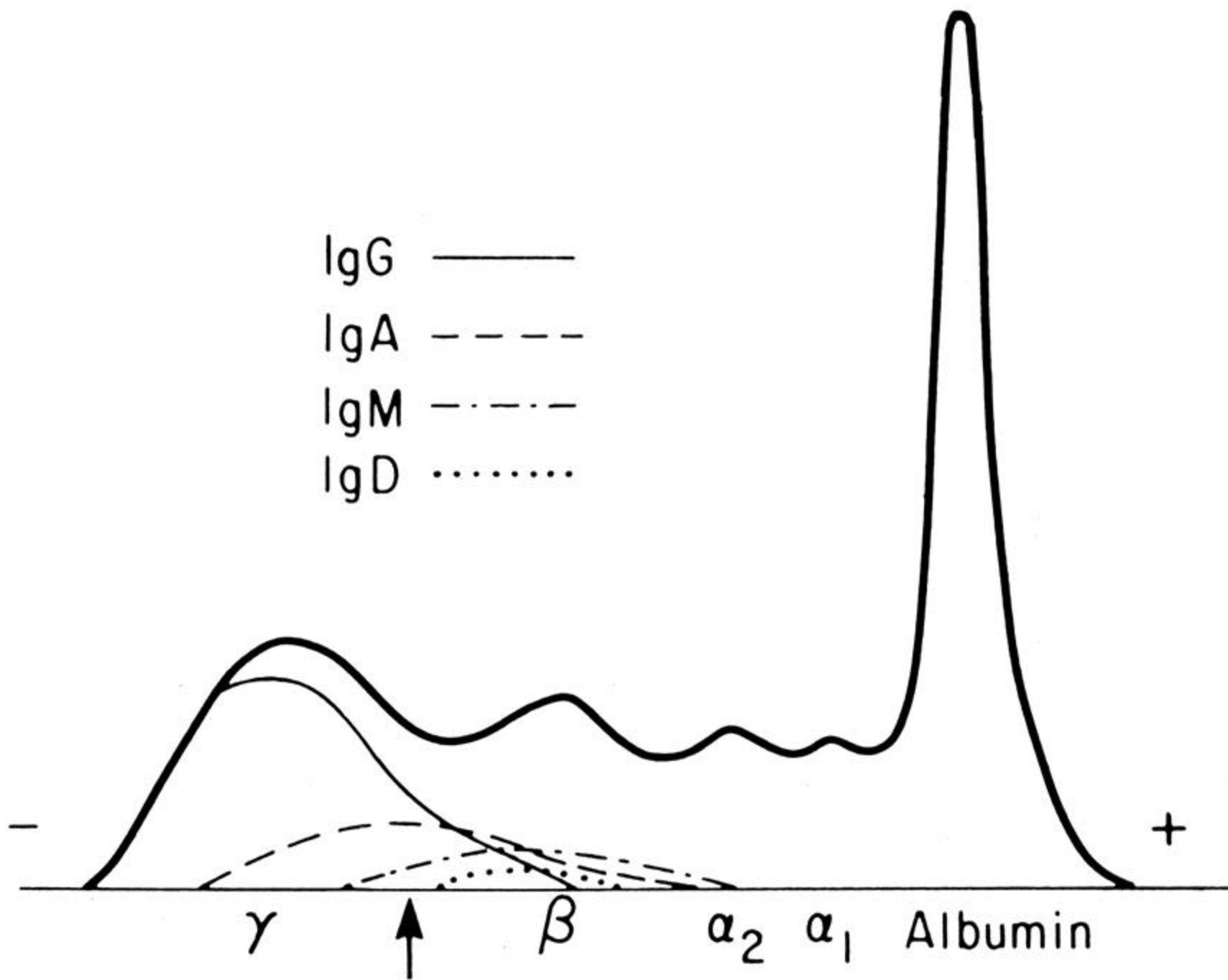
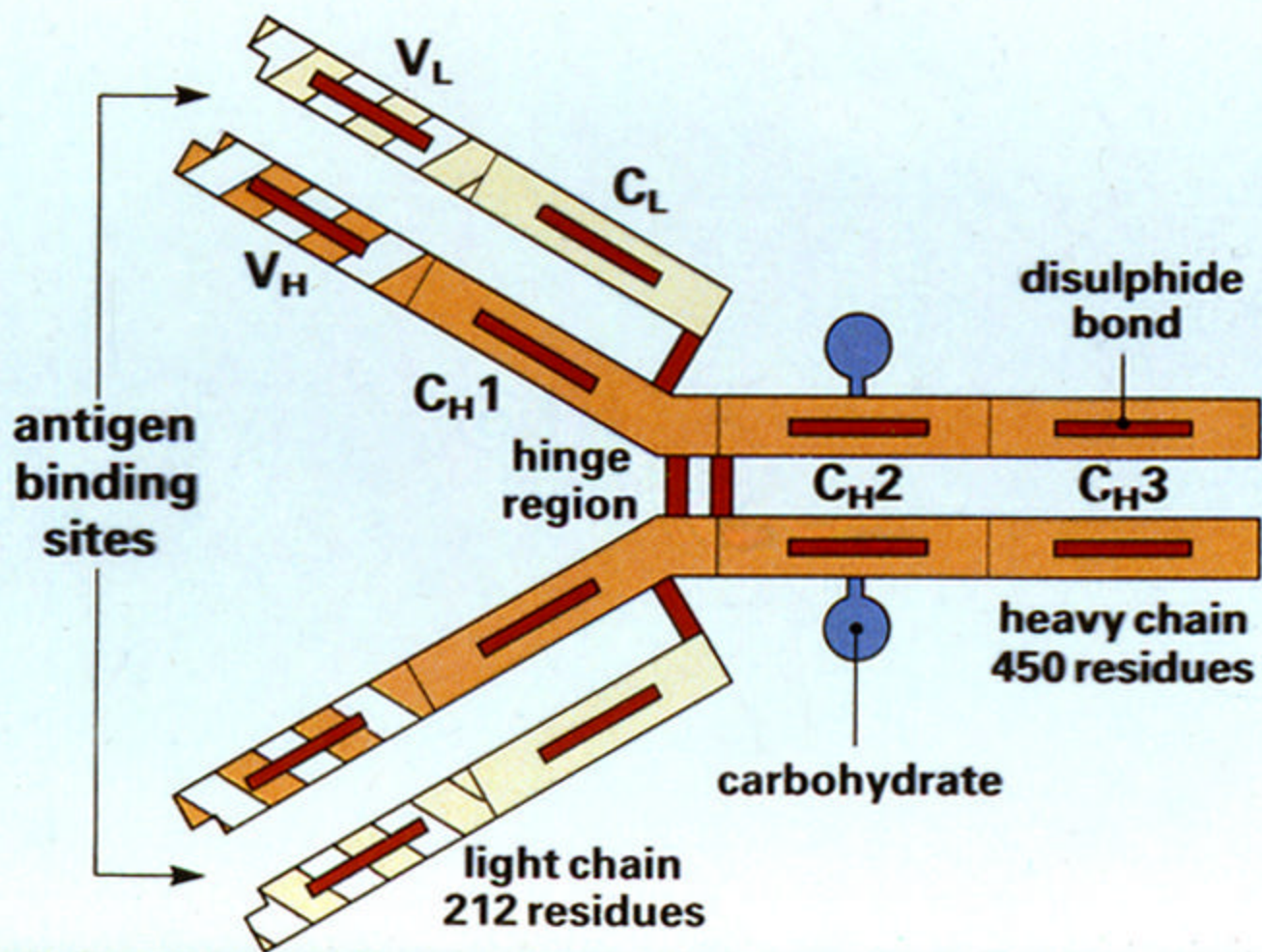


Immunoglobulin Tx

- 1890: Report by v.Behring and Kitasato
Diphtheria- und Tetanus-Immunity
- 1936: Tiselius/Kabat, Ab in gammaglobulin
- 1940s: Edwin Cohn: plasma fractionation
- 1953: Bruton, discovers XLA and Ig-Tx
- 1962: Barandun gives IVIG
- 1981: IVIG approved in US



The basic structure of IgG





DESIRABLE IGIV ATTRIBUTES

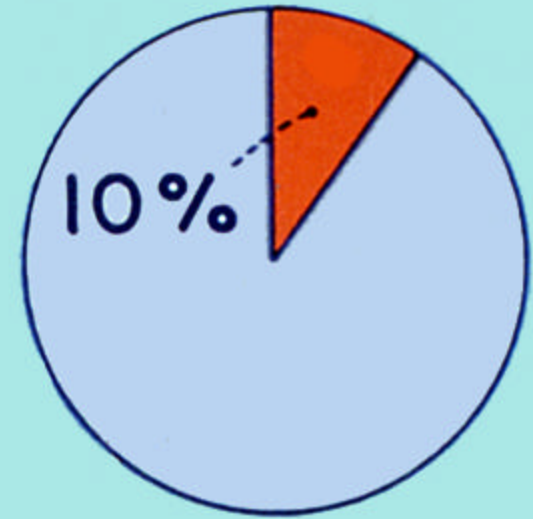
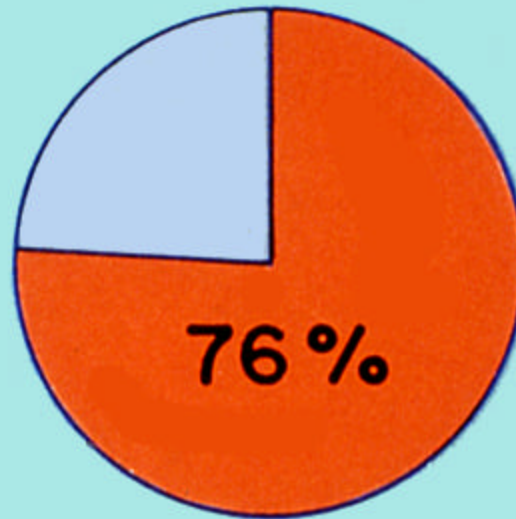
- Highly purified IgG
- Free of preservatives
- Free of infectious agents
- Monomeric (free of aggregates)
biologically active (native)
- Normal distribution of IgG Subclasses
- Broad spectrum of antibody activity

INCIDENCE OF SIDE EFFECTS

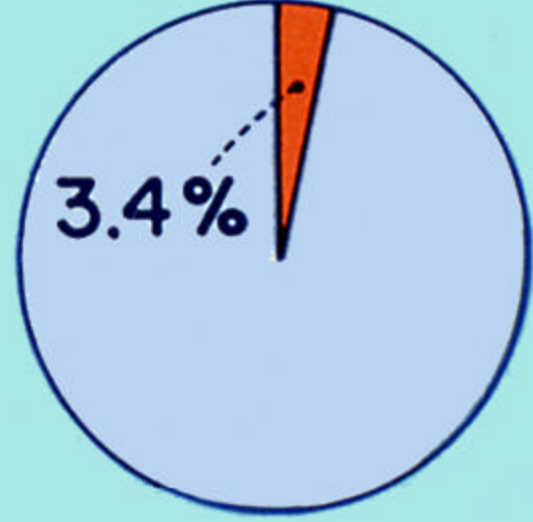
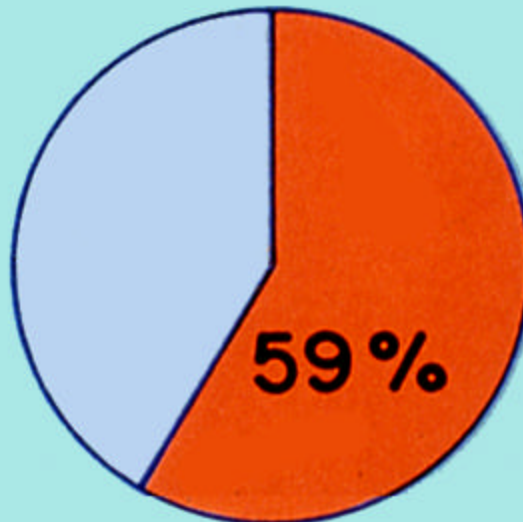
MIG
0.3 M Glycine

MIG
10 % Maltose

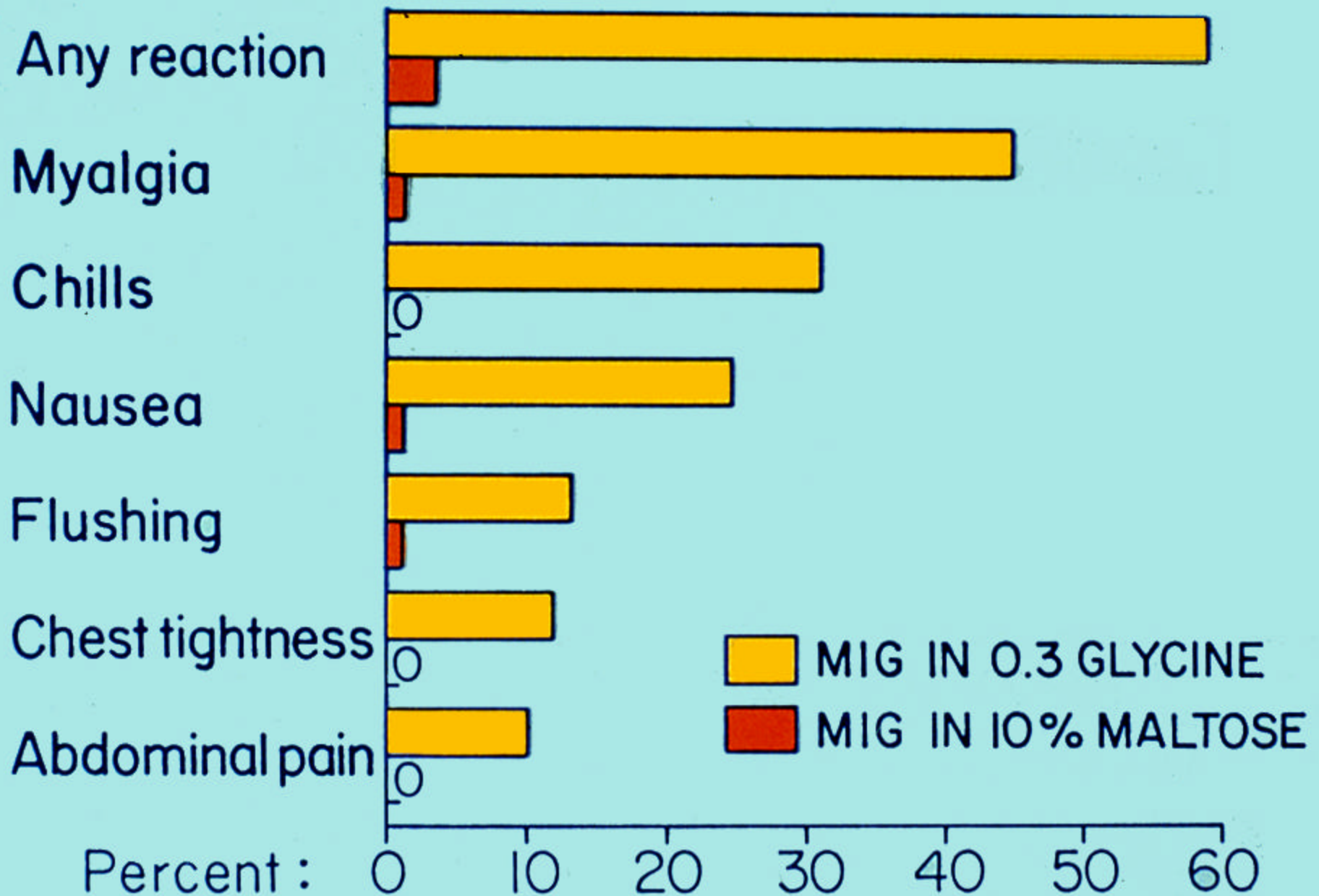
Number of patients
with side effects
(total 27 patients)



Number of infusions
with side effects
(total 87 infusions)



% INFUSIONS WITH SIDE EFFECTS



O. D.
0.02

MIG-MALTOSE 61°C

O. D.
0.05

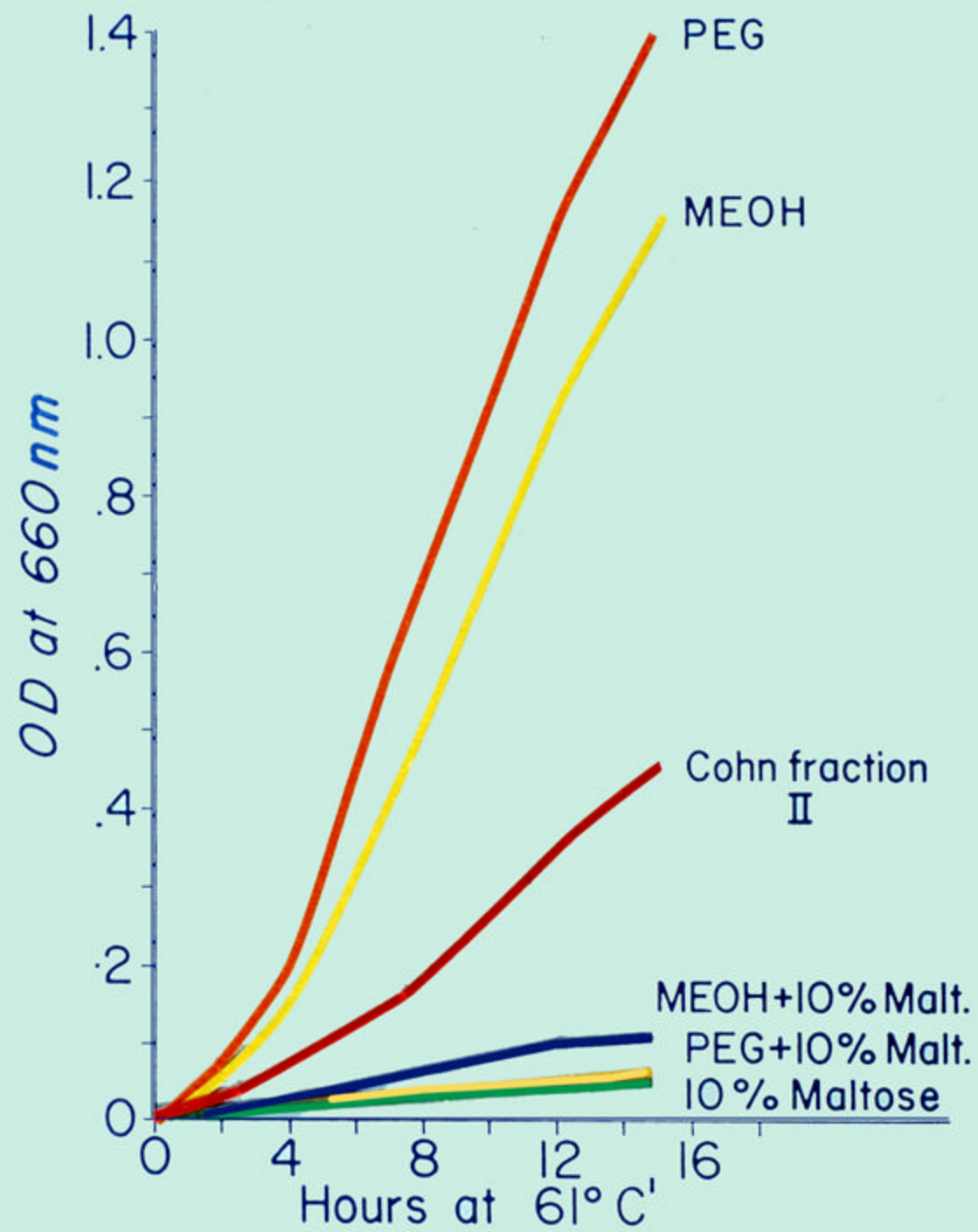
CFII IN MALTOSE 61°C

O. D.
0.92

CFII, 61°C

O. D.
0

CFII, 20°C



IVIG

Therapeutic action

- Replacement therapy
- Anti-inflammatory agent
- Induction of Fc receptor blockade
- anti-idiotypes autoimmune phenomena
- Binding of activated complement components

IVIG: Primary IDS (1)

- XLA
- Hyper IgM syndromes
- CVID
- IgG subclass deficiencies
(associated with Ab-def.)
- SCID

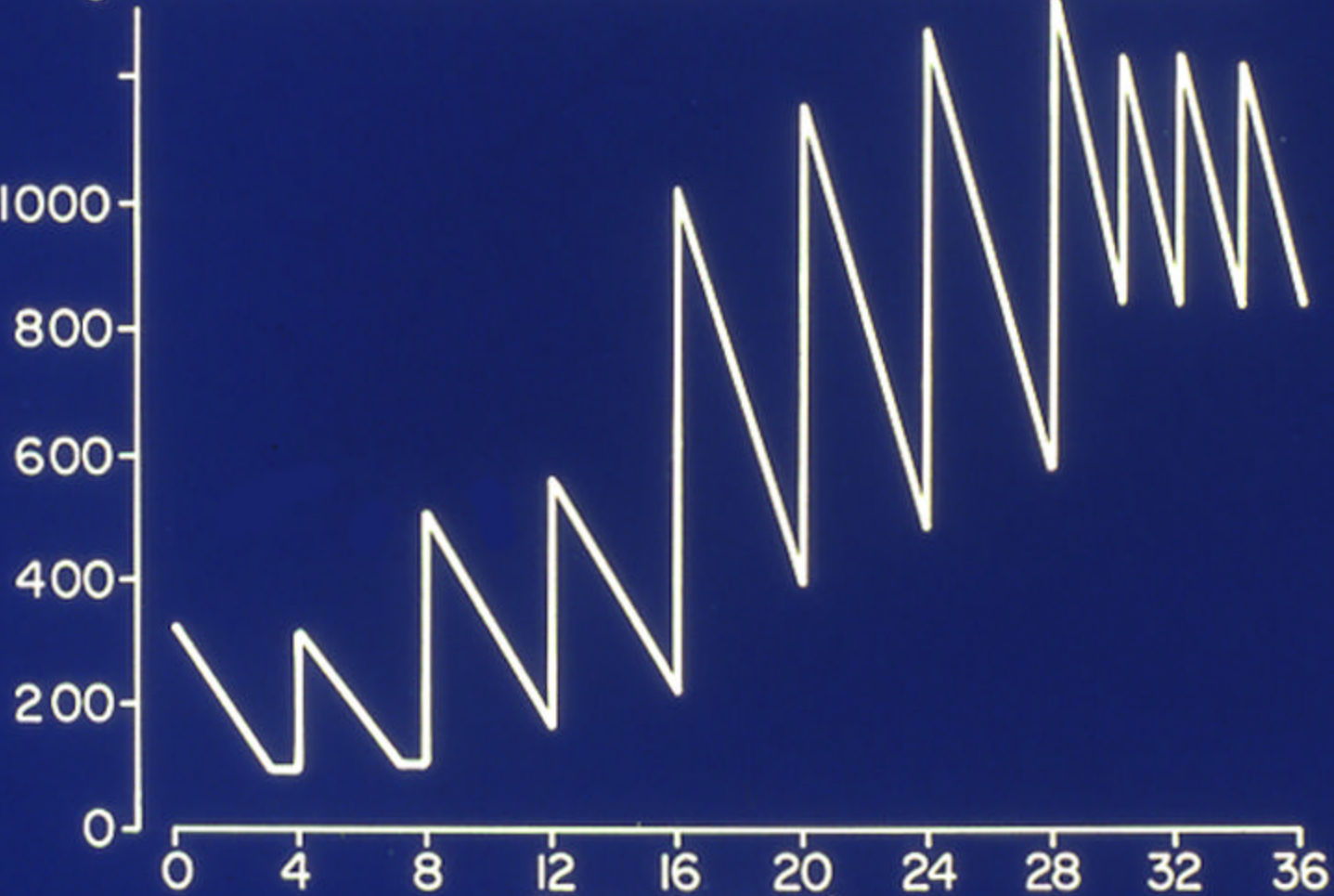
IVIG
mg/kg

400
300
200
100
0

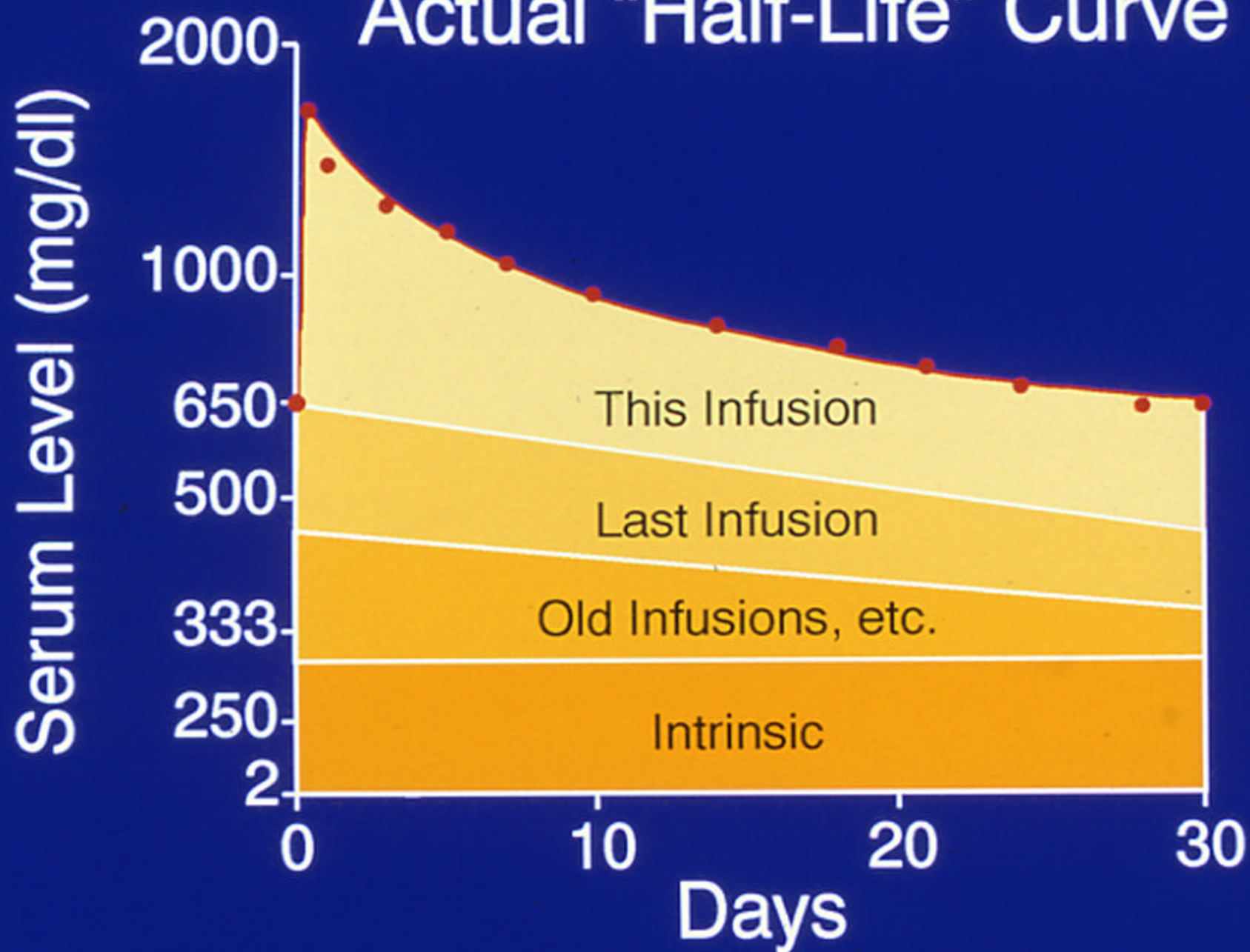
Serum IgG
mg/dl

1000
800
600
400
200
0

0 4 8 12 16 20 24 28 32 36
Time (weeks)



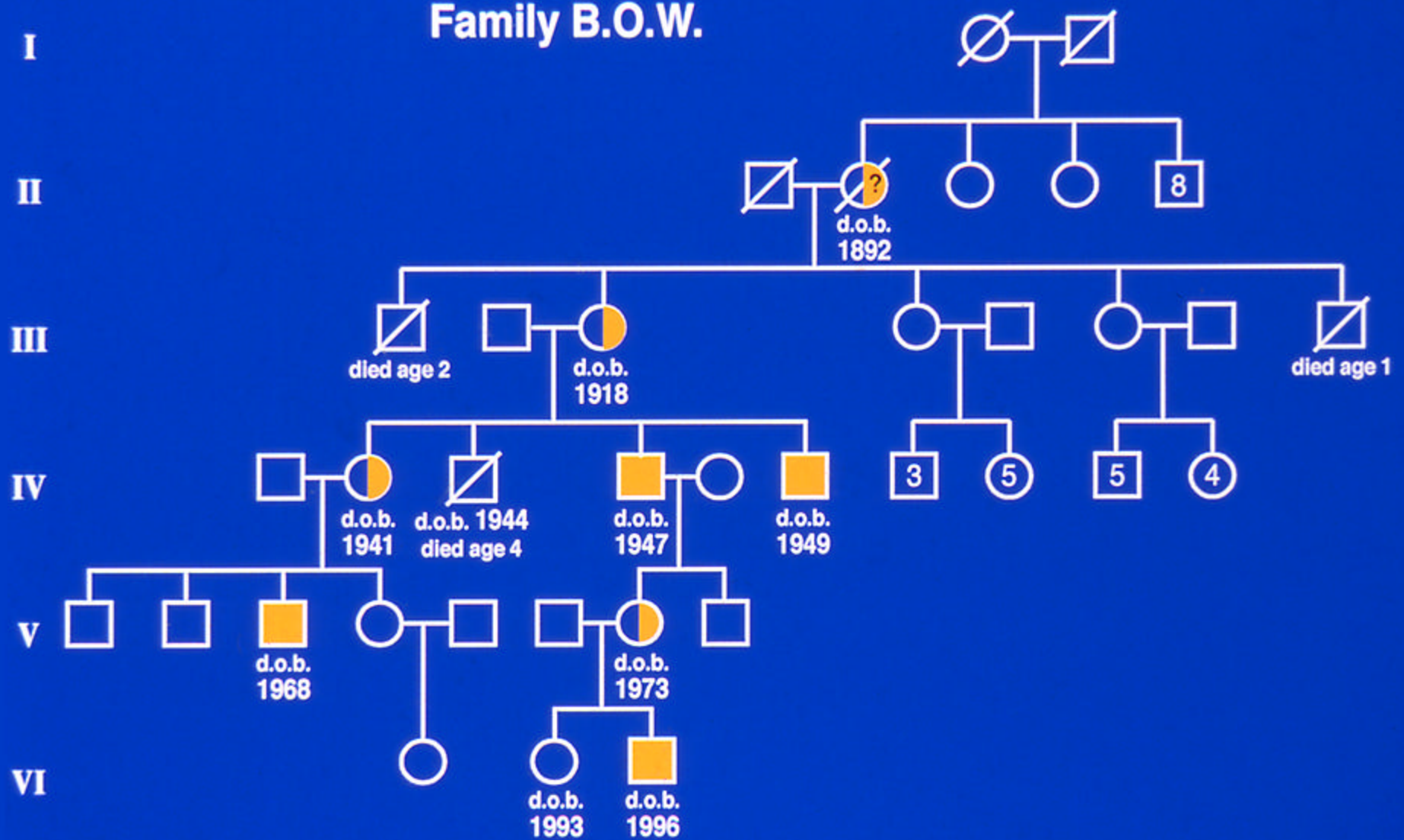
Actual "Half-Life" Curve



Serum IgG - Concentration

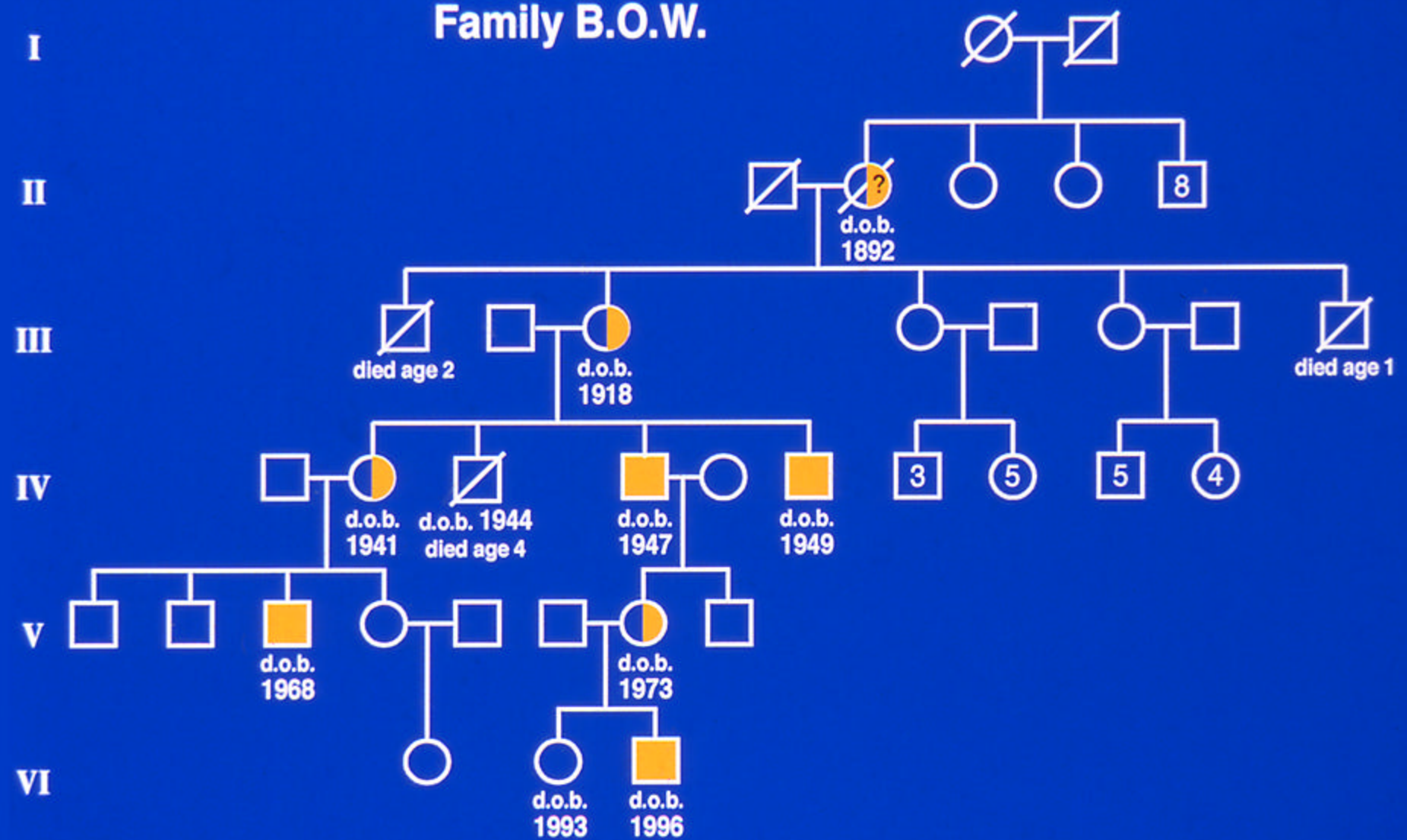
- Dose (mg/Kg)
- Route of injection: IV, IM, SQ
- Frequency of infusion
- Peak level
- Catabolic rate
- Losses
- Hydration, edema
- T 1/2 of preparation

Family B.O.W.





Family B.O.W.

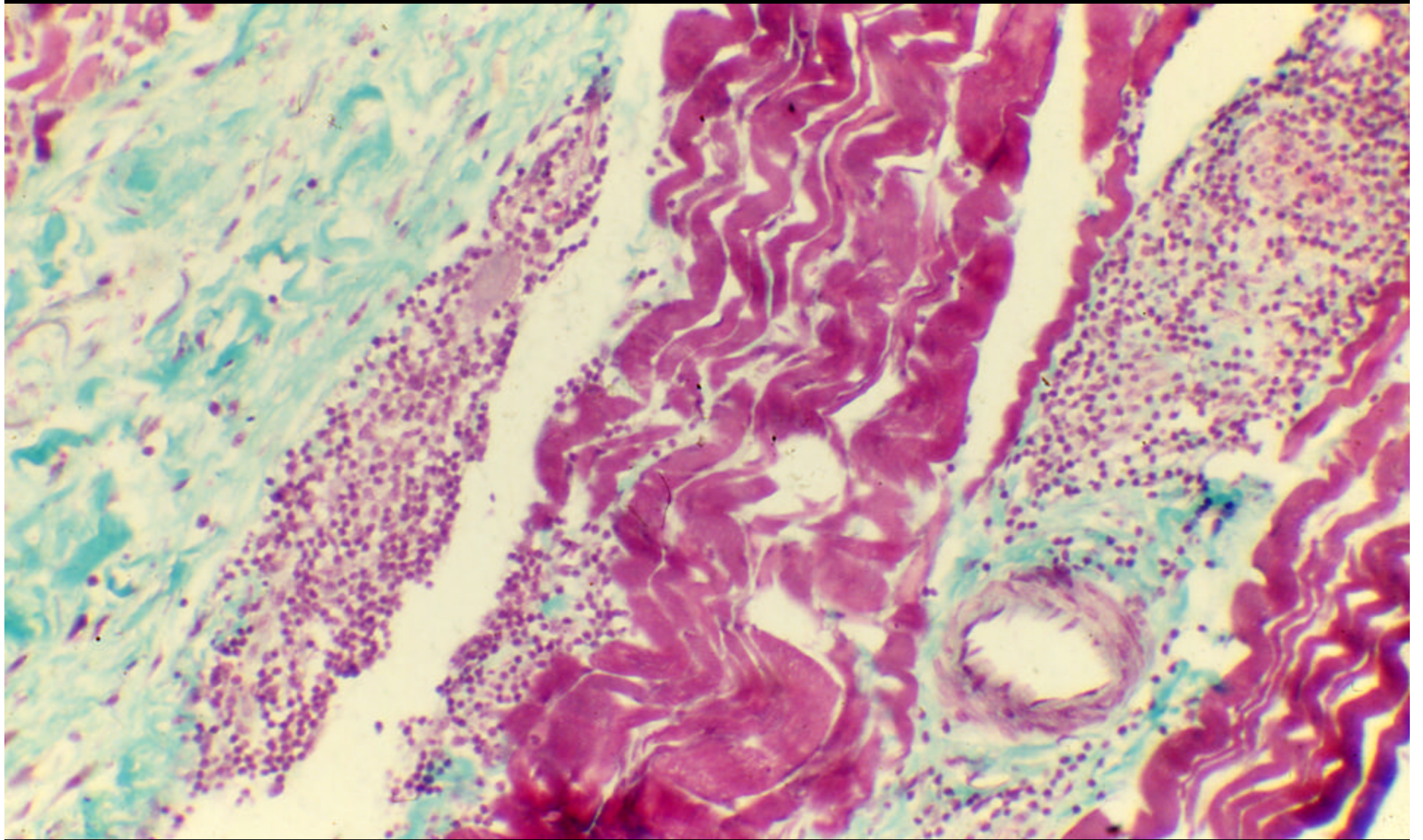


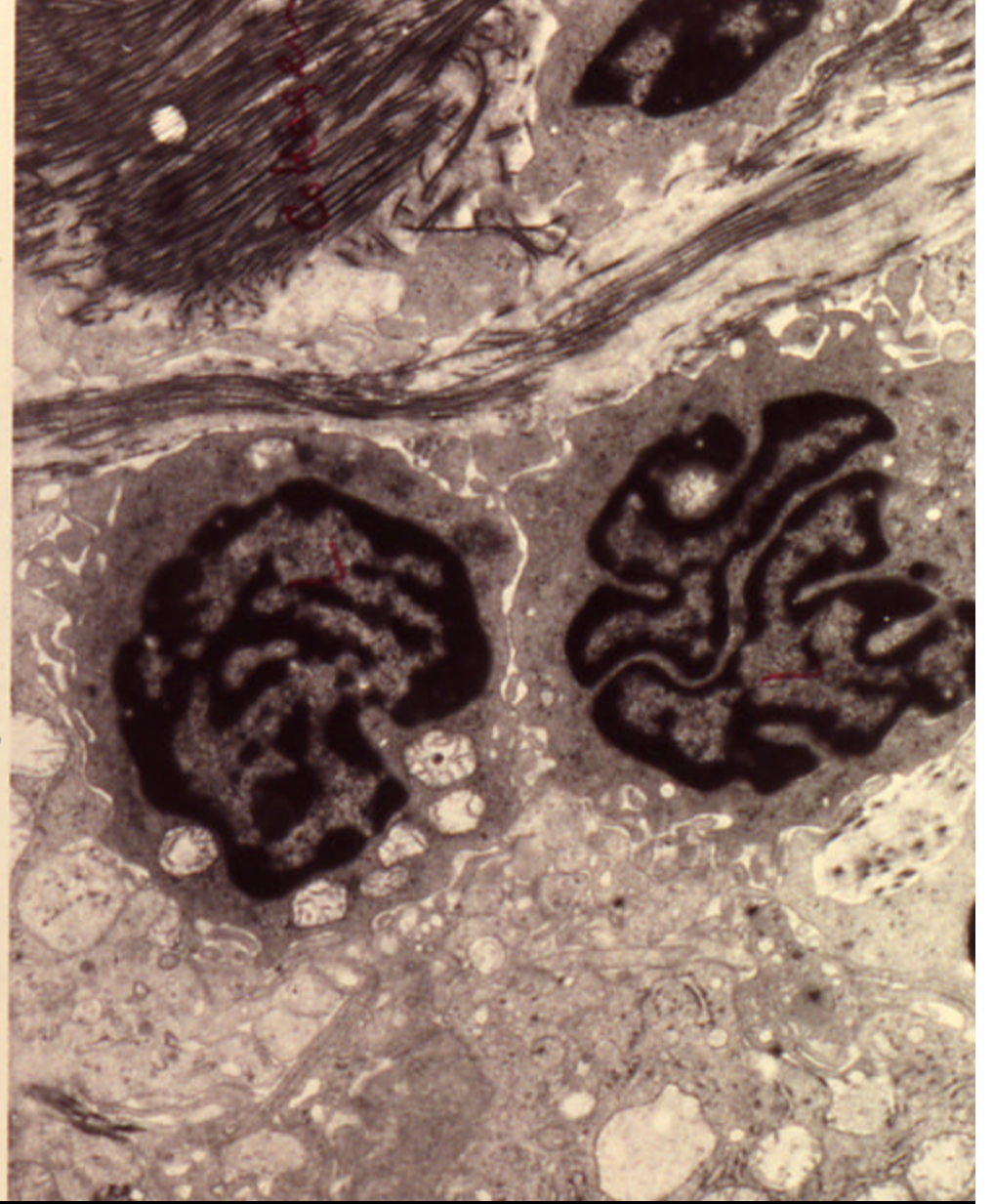
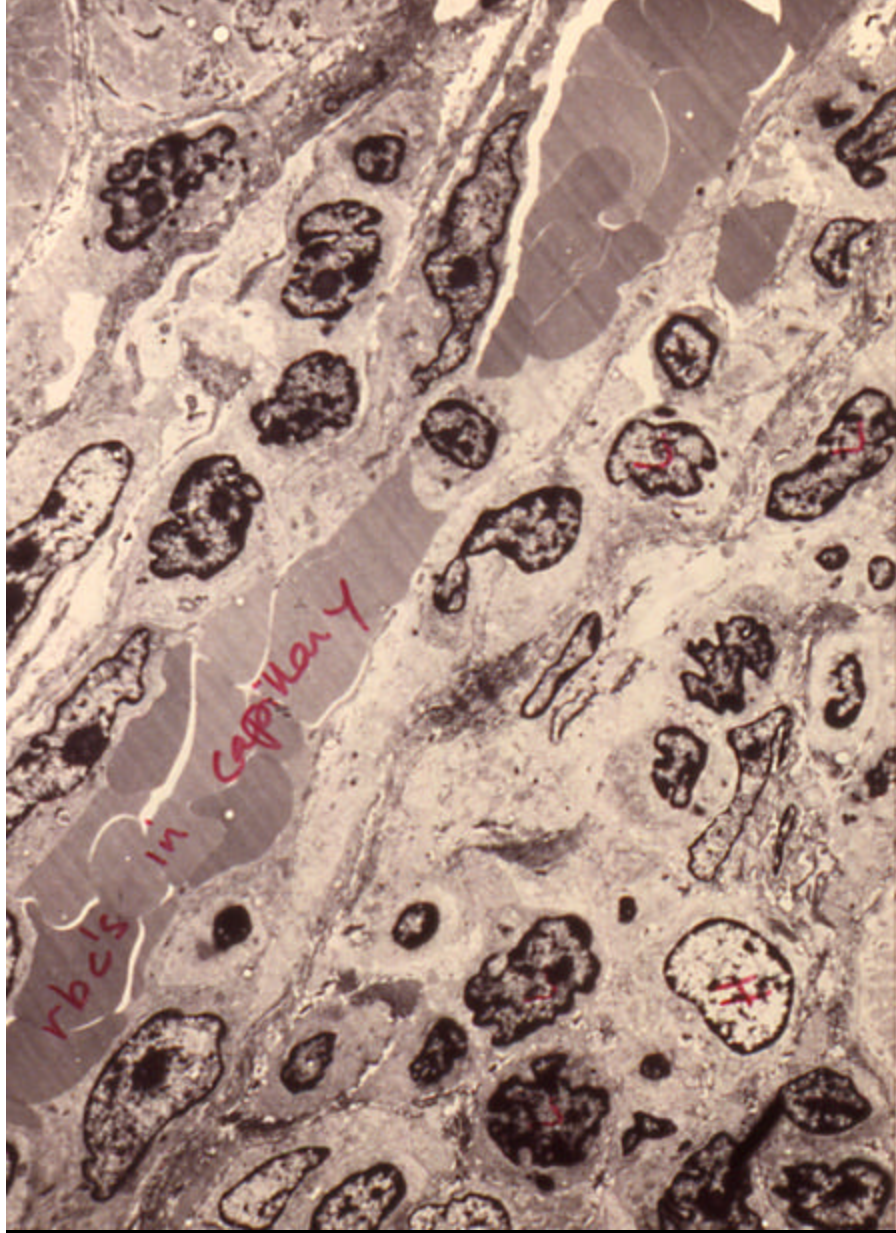
ECHO — INFECTION IN XLA

- slowly progressive CNS-symptoms
 - ataxia, cognitive skills
 - parasthesia, seizures
 - dermatomyositis—like
 - myositis/fasciitis
- 1 CPK, SGPT, Alk. phosph.

ECHO — INFECTION IN XLA

- 1990 survey: 34 centers
- 248 XLA observed
- incidence of ECHO infection:
 - before 1985: 39
 - after 1985: 4
 - (3 atypical, 1 untreated)





IVIG – Safety (1)

Free of infectious agents

(HCV, HBV, HIV, parvo, prions)

No aggregates

pH

Osmolality

Low IgA (?)

Limit the rate of infusion

Reduce interval between infusions

IVIG – Safety (2)

Antiviral steps (at least 3)

Viral partitioning

 cold ethanol fractionation

Antibody causes viral neutralization

Low pH

β -propiolacton or Caprylate treatment

Solvent/Detergent

Pasteurization

Nanofiltration

UV

IVIg – adverse events (1)

General reactions – common

Anaphylaxis – extremely rare

Acute renal failure

Cardio-vascular

volume

thrombotic events

Coombs-positive hemolytic anemia

CNS- aseptic meningitis

IVIg – adverse events (2)

General reactions

- * 1st infusion
- * infusion when patient is infected
- * rate related
- * infusion interval related
- * Product related

IVIG – 1st infusion

High rate of common adverse events

Infuse at center, MD present

IgG dose: 400 mg/kg weight

vital signs, Tylenol 600mg(adult)

IgG infusion rate: 30 mg/Kg/hr – 30'

60 mg/Kg/hr – 30'

120 mg/Kg/hr – 30'

then 150 – 200 mg/Kg/hr

if reaction: 100mg Solucortef IV

or 40 mg Solumetrol IV

Benadryl 50mg IV

IVIg – 2nd infusion

Infuse in center, 2 weeks after 1st dose
dose 400 mg/kg weight

If reaction during 1st infusion –
vital signs, pretreat with Tylenol 600mg
+/- hydrocortisone

IgG rate : 30mg/Kg/hr – 30'

60mg/Kg/hr – 30'

120mg/Kg/hr – 30'

then 150-200mg/Kg/hr

IVIg – subsequent infusions

Dose : 400mg/Kg/4 weeks
or 300mg/Kg/3 weeks
or 200mg/Kg/2 weeks

+/- Tylenol

Rate 60mg/Kg/hr – 30'
then 150-200(250 max)mg/Kg/hr

IVIg dosing (1)

Know baseline IgG level

Trough level 350-500mg/dl above baseline

increase dose (or shorten interval) if

IgG level drops

progressive pulmonary disease

pre infusion “blues”

weight gain

problems with adverse events

IVIg dosing (2)

Individual dosing

Does 600-800mg/Kg provide better protection?

Yes: Cunningham-Rundles C, 1984

Roifman CH, 1987

Bernatowska E, 1987

Liese JG, 1992

Eijkhout HW, 2001

Frequent vs. infrequent infusions

Peak – trough or area under the curve

IVIg – which preparation?

Does it make a difference?

3% vs 5 or 6%, vs 10(12)%, (vs 16%)

Lyophilized or liquid?

Osmotic load

Viral inactivation steps

IgA level

Antibody titers

Source vs Recovered plasma

Plasma units per IVIg-batch

IVIg – Infusion Schedule

Monthly dose

every 4 weeks

75% every 3 weeks

50% every 2 weeks

Infusion center

At home by a nurse

Self infusion at home

cost, quality of life

IVIIG – Self infusion at home (1)

Selected patients

Pro: patient becomes partner

flexible dosing

frequent infusions

q 2 weeks: no AE

overall AE: 0.7 – 0.8% (Brennan V.M., 2003)

? Quality of Life

Con: Supervision

May miss complications

legal



IVIg – Self infusion at home (2)

Rules: chaperon present
 contact Medical Center if problems
 keep diary
 know where to go if access problem
 to be seen by Center q 6-12 months
 (full exam, CBC, IgG trough level,
 liver tests, Pulmonary Function, CT

Subcutaneous IgG infusions (1)

Sweden >90%

Britain ~ 30-50%

USA clinical trials completed

pro: self infusion at home

easy access, consistent IgG levels

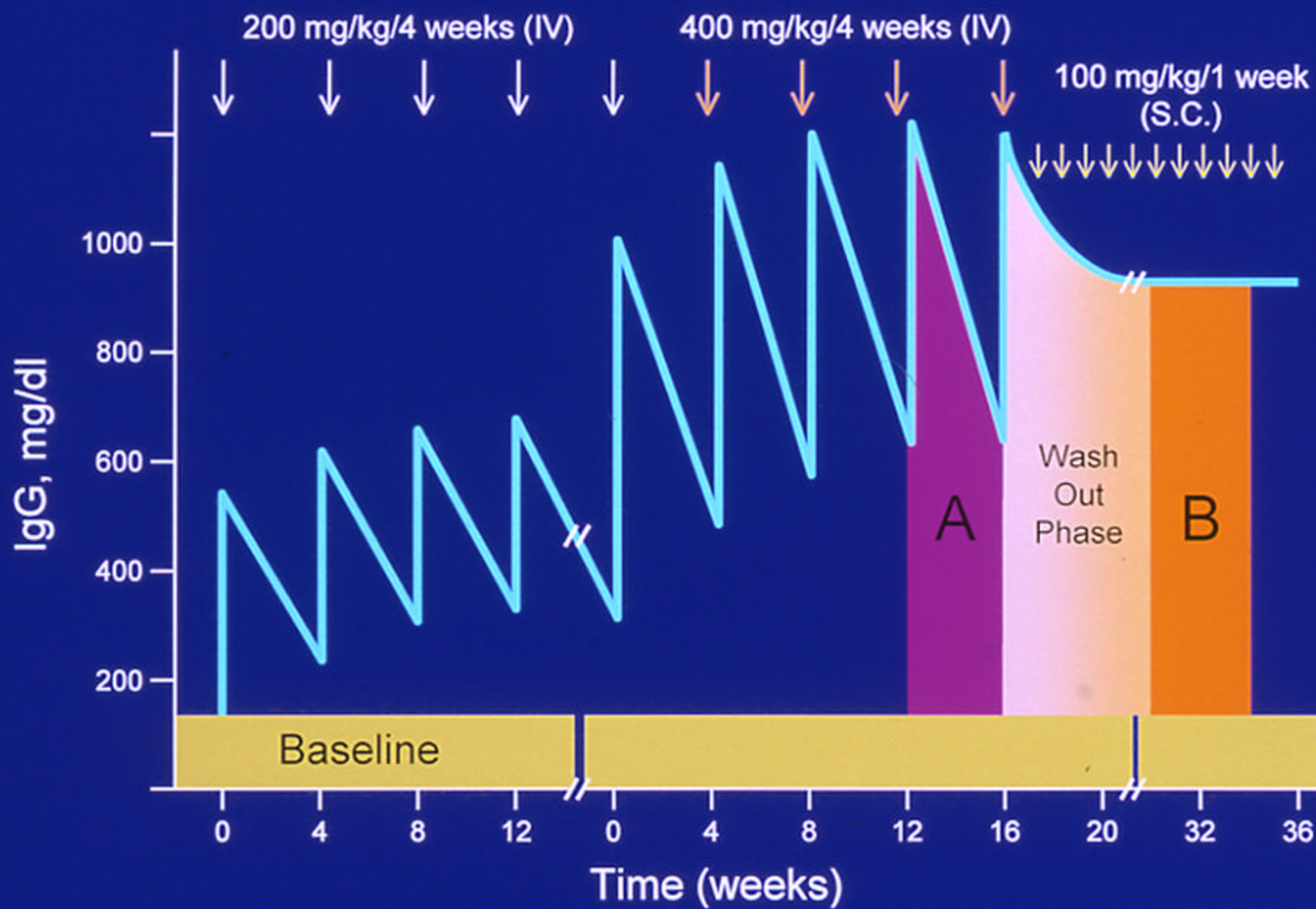
minimal adverse events(mild)

(106 per 27000 infusions)

less costly

con: Supervision?

local reactions



Subcutaneous IgG infusions (2)

Instruction how to self infuse

Product: 16% IgG in Glycine buffer

Dose: 100mg/Kg/week

Site: abdomen or thigh, 25G needle, EMLA cream

Provide pump, best a syringe driver

infusion time 1 hour (30-90min)

or 20 – 35 ml/hr/2 sites

15-20 ml/site

No pre-medication

Ok for infants (direct push)

IVIG/SQIG – safety monitoring

Record lot #

Every 6-12 months:

- IgG trough level

- transaminases

- (HCV by PCR?)

- (archive serum?)

- CT Scan yearly

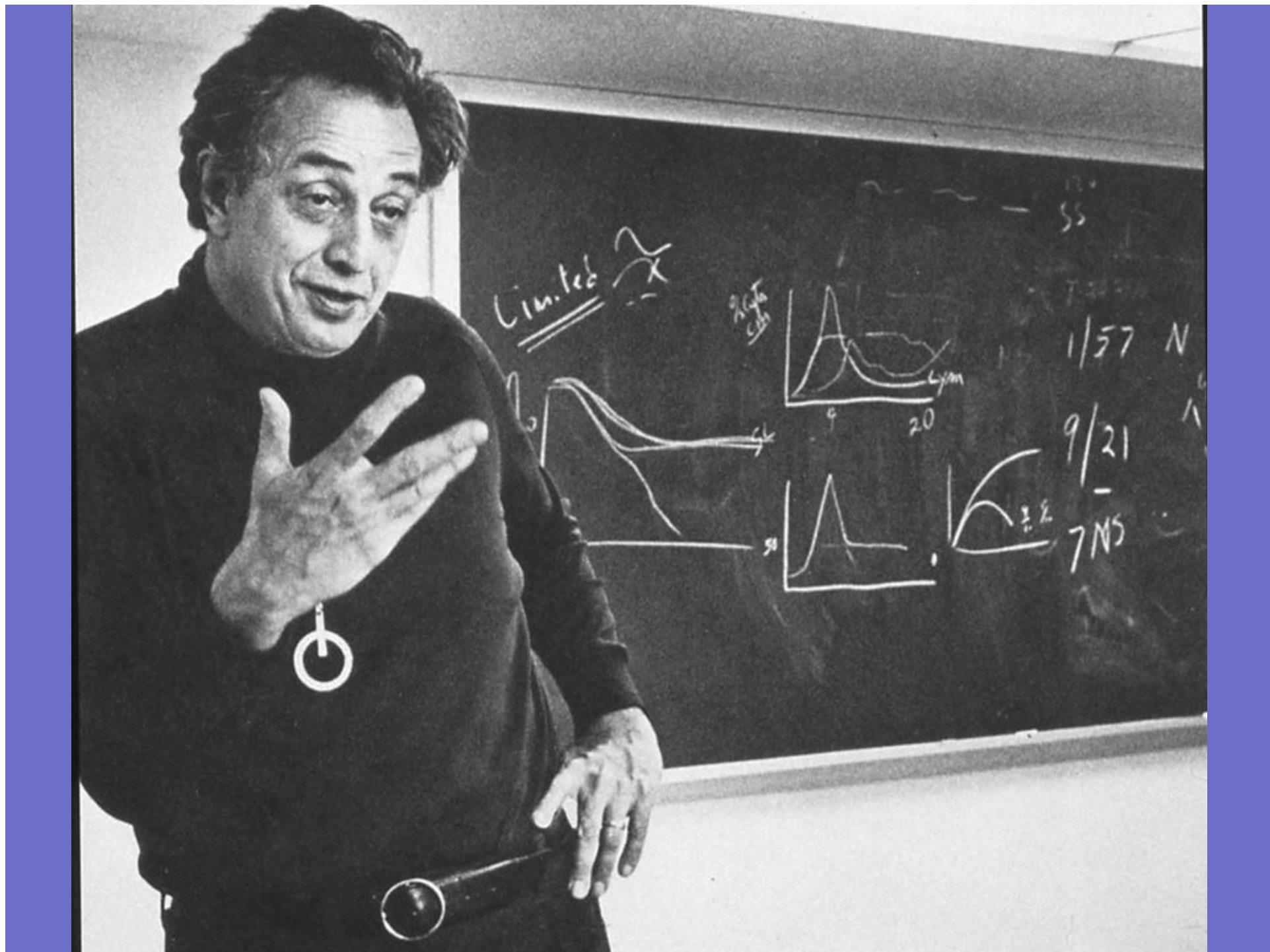
IVIIG - preparations

Baxter	Bayer	ZLB-Behring	Octapharma
Gammagard S/D	Gamunex	Gammar-P	Octagam
Lyophilized	Liquid	Lyophilized	Liquid
IgG 5%/10%	10%	5/10%	5%
mOsm/l 636-1250	258	309-600	310-180
2% glucose	no sugar	5% sucrose	10% maltose
pH 6.8	4.0-4.5	6.8	5.1-6.0

Also: Grifols: Flebogamma, 5%, liquid, 5% D-sorbitol, 240-350 mOsm/l

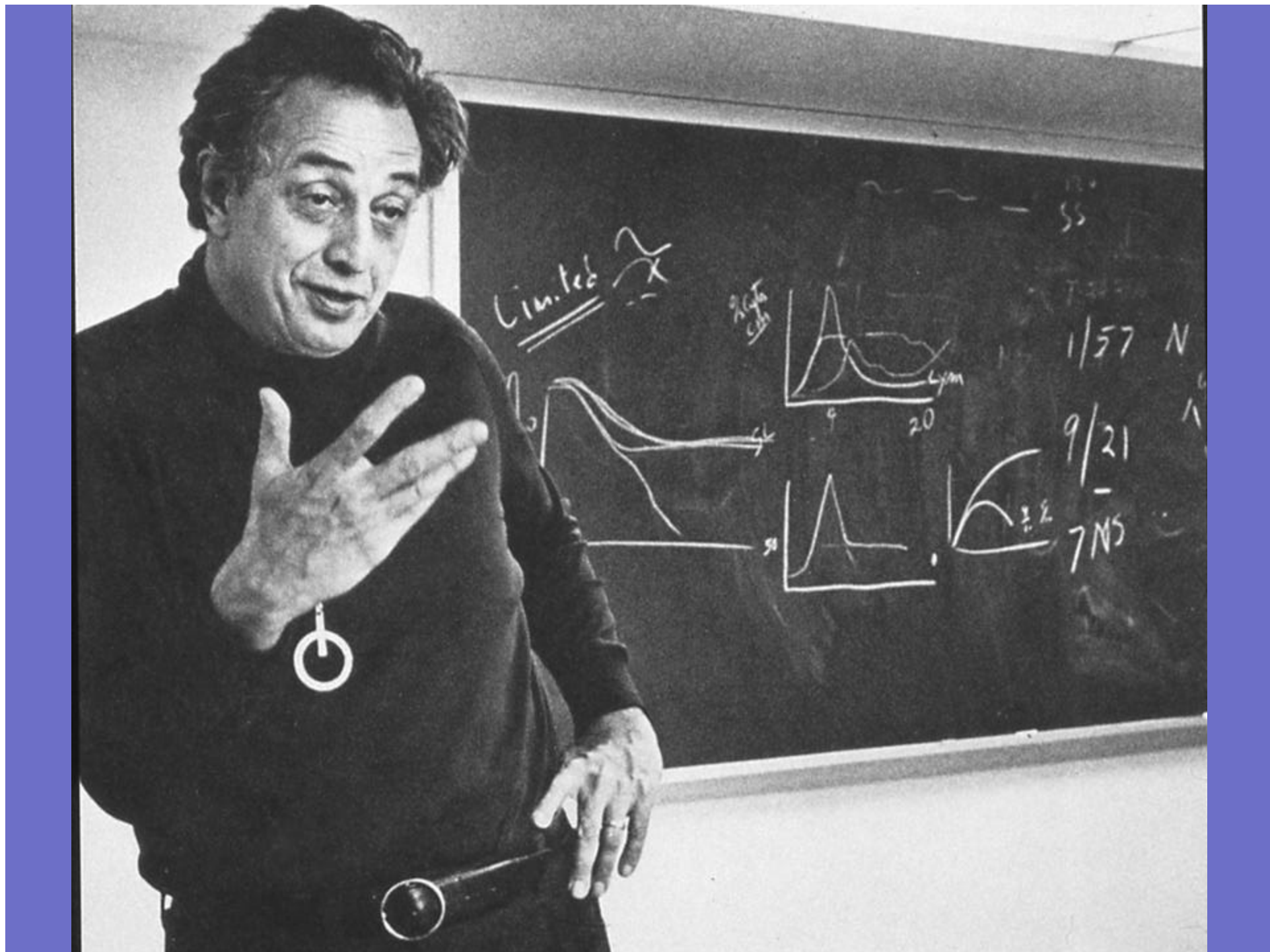
ZLB-Behring: Carimune, 3-12%, lyophilized, 0-6% glucose,
142-768 mOsm/l - replaces Sandoglobin





Future Issues

- Safety: Prions
- Availability: Industry-FDA-Patients-Doctors
- Ig formulation: liquid, lyophi., osmolality, IgG concentration, sugar?
- Role of spiking: Hyperimmune, mAb
- Infusion choice: IV, SQ, (IM)
- Simplify: self infusion, at home, q.4weeks, weekly, q. day – can we save \$?



SIDE EFFECTS OBSERVED DURING INFUSION OF MIG IN .3M GLYCINE AND MIG IN 10% MALTOSE

• • •Type of reaction	No. (%) of infusions with side effects	
	MIG	MIG-Maltose
• Total reactions	51 (59%)	3 (3.4%)
• Pain (joints, back, • Muscle)	39 (45%)	1 (1%)
• Chills	27 (31%)	0
• Nausea	22 (25%)	1 (1%)
• Flushing	11 (13%)	1 (1%)
• Chest tightness	10 (12%)	0
• Abdominal cramps	10 (12%)	0
• Anxiety	7 (8%)	0
• Wheezing	5 (6%)	0

IVIIG – adverse events (3)

Acute renal failure

- > 65 years, diabetic

- preceding renal disease

- 90% received sucrose containing IVIG

- bx: high solute load damage of proximal tubule
(osmotic nephrosis)

- reversible

Avoid sucrose containing IVIG in at risk patients

MMR 48(24):518, 1999

IVIIG – adverse events (4)

Cardio-vascular complications

- * Volume and rate of infusion ? heart failure
- * Thrombotic events
- * Secondary to ? viscosity, ? bloodflow
- * Myocardial infarct, stroke

IVIG – Adverse events (5)

Coombs-positive (direct)
shortly after IVIG infusion
rarely associated with hemolytic anemia
secondary to IgG anti-A/B
related to IVIG dose
no action required

IVIIG – adverse events (6)

Neurologic complications

- * headache, dose dependent
- * aseptic meningitis
 - headache, fever,
 - meningism, nausea + vomiting
 - +/- eosinophilia
 - may recur
- * thrombotic event - stroke